VOLUME 27 · NUMBER 2 · JANUARY 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Phase II Study of Pulse Erlotinib Before or After Carboplatin and Paclitaxel in Current or Former Smokers With Advanced Non–Small-Cell Lung Cancer

Gregory J. Riely, Naiyer A. Rizvi, Mark G. Kris, Daniel T. Milton, David B. Solit, Neal Rosen, Emir Senturk, Christopher G. Azzoli, Julie R. Brahmer, Francis M. Sirotnak, Venkatraman E. Seshan, Margaret Fogle, Michelle Ginsberg, Vincent A. Miller, and Charles M. Rudin

From the Thoracic Oncology Service, Departments of Medicine, Radiology, and Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, Weill Medical College of Cornell University, New York, NY; and the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medical Institutions, Baltimore, MD.

Submitted March 31, 2008; accepted August 26, 2008; published online ahead of print at www.jco.org on December 1, 2008.

Presented in part at the 43rd Annual Meeting of the American Society of Clinical Oncology, June 1-5, 2007, Chicago, IL

Supported in part by Genentech, Inc.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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Corresponding author: Gregory J. Riely, MD, PhD, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10022; e-mail: rielyg@mskcc.org.

0732-183X/09/2702-264/$20.00

DOI: 10.1200/JCO.2008.17.4656

ABSTRACT

Purpose
A prior study demonstrated that addition of continuous daily erlotinib fails to improve response rate or survival in non–small-cell lung cancer (NSCLC) patients treated with carboplatin and paclitaxel. However, preclinical data support the hypothesis that intermittent administration of erlotinib before or after chemotherapy may improve efficacy. We tested this hypothesis in patients with advanced NSCLC.

Patients and Methods
Eligible patients were former or current smokers with chemotherapy-naive stage IIIB or IV NSCLC. All patients received up to six cycles of carboplatin (area under the curve = 6) and paclitaxel (200 mg/m^2), with random assignment to one of the following three erlotinib treatments: erlotinib 150 mg on days 1 and 2 with chemotherapy on day 3 (150 PRE); erlotinib 1,500 mg on days 1 and 2 with chemotherapy on day 3 (1,500 PRE); or chemotherapy on day 1 with erlotinib 1,500 mg on days 2 and 3 (1,500 POST). The primary end point was response rate.

Results
Eighty-six patients received treatment. The response rates for the 150 PRE, 1,500 PRE, and 1,500 POST arms were 18% (five of 28 patients), 34% (10 of 29 patients), and 28% (eight of 29 patients), respectively. The median overall survival times were 10, 15, and 10 months for the 150 PRE, 1,500 PRE, and 1,500 POST arms, respectively. The most common grade 3 and 4 toxicities were neutropenia (39%), fatigue (15%), and anemia (12%). Grade 3 and 4 rash and diarrhea were uncommon.

Conclusion
Patients treated on the 1,500 PRE arm had the highest response rate and longest survival, with ranges similar to those reported for carboplatin, paclitaxel, and bevacizumab in a more restricted population. Further evaluation of this strategy in a phase III trial is proposed.

J Clin Oncol 27:264-270. © 2008 by American Society of Clinical Oncology

INTRODUCTION

The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib were the first targeted agents to demonstrate reproducible, single-agent activity against non–small-cell lung cancer (NSCLC).[1-4] Preclinical data suggested that combining the EGFR TKI with chemotherapy would lead to a synergistic antitumor response.[5,6] In four clinical trials that enrolled more than 4,000 patients, erlotinib and gefitinib were individually combined with either carboplatin and paclitaxel or gemcitabine and cisplatin. Each of these trials showed no benefit in any common efficacy end point when either gefitinib or erlotinib was added to these chemotherapy doublets.[7-10] These trials, designed before the identification of clinical and molecular factors that can predict response to single-agent erlotinib or gefitinib, were conducted in unselected populations of patients with metastatic NSCLC.[11-14] Analysis of the never-smoker subset of patients in the TRIBUTE trial (carboplatin, paclitaxel, ± erlotinib) demonstrated that never smokers treated with erlotinib had a longer overall survival compared with patients who had received only chemotherapy, a result now being studied in a randomized trial by the Cancer and Leukemia Group B.[8]

Several studies have suggested that giving an EGFR TKI continuously with chemotherapy may be inferior to other approaches that separate the administration of chemotherapy and EGFR TKI. Exposure of EGFR wild-type cell lines to gefitinib

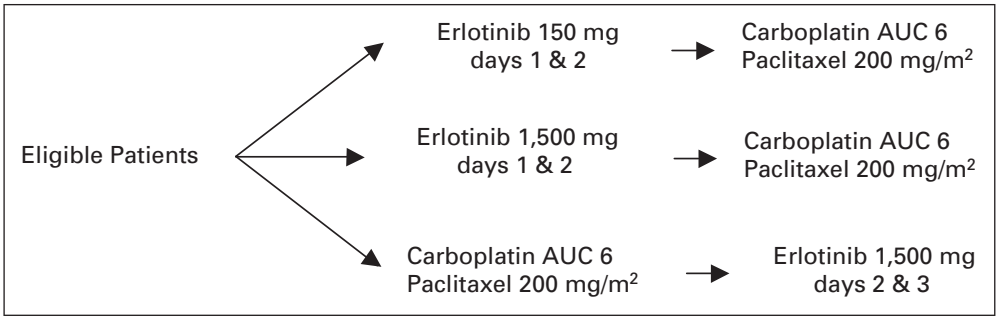

Fig 1. Trial schema. AUC, area under the curve.

or erlotinib leads to G_1 arrest.[15] It has been postulated that cells in G_1 may be resistant to the effects of chemotherapy, which leads to apoptosis preferentially in cells that are in the G_2 or M phase of the cell cycle. Additional preclinical work suggests that alternate schedules of EGFR TKIs in combination with chemotherapy could augment the effects of chemotherapy. Solit et al[16] used a human tumor xenograft model of NSCLC with wild-type EGFR to demonstrate that administering pulsatile gefitinib before paclitaxel leads to more tumor shrinkage than either agent alone or the combination when gefitinib is administered on a continuous daily schedule. The greatest tumor inhibition was seen in animals treated with high doses of gefitinib for 2 days before receiving paclitaxel. In contrast, others have used cell lines in vitro to show that cells treated with erlotinib after docetaxel had the greatest evidence of cytotoxicity.[17,18] Taken together, these data suggest that altering the dose and schedule of EGFR TKIs in combination with chemotherapy could improve the efficacy of the combination of these agents. These effects have been observed in tumors that do not harbor *EGFR* mutations or amplification, which are abnormalities that, in and of themselves, are associated with sensitivity to gefitinib or erlotinib.

To provide data to test the hypothesis that higher, intermittent dosing of erlotinib could lead to significant increases in the response rate of patients receiving carboplatin and paclitaxel, we conducted a randomized phase II trial in which erlotinib was administered before or after chemotherapy in patients with advanced NSCLC. We have previously demonstrated the safety of administering intermittent high doses of erlotinib alone (up to 2,000 mg),[19] as well as the safety of administering gefitinib 2,250 mg in combination with docetaxel.[20] The preclinical work supporting high doses of erlotinib before taxane chemotherapy used the animal model maximum-tolerated dose for gefitinib in combination with chemotherapy.[16] In this trial, we used erlotinib 1,500 mg to explore this hypothesis in patients. The primary goal of this phase II study was to evaluate the objective response rate and toxicity of three different treatment schedules of erlotinib in combination with carboplatin and paclitaxel as first-line therapy in patients with advanced NSCLC to identify an optimal schedule for testing in future phase III studies. We used the same eligibility criteria, exclusion criteria, treatment plan, chemotherapy dose modifications, and evaluations used in TRIBUTE.[8] We felt that this would allow us to compare our results to an historical benchmark treating similar patients with chemotherapy alone.

PATIENTS AND METHODS

Patients

All patients had clinical stage IIIB or IV or recurrent, pathologically confirmed NSCLC of any histology. Patients had received no prior chemotherapy, and it had been at least 3 weeks since any prior radiation therapy. All patients had Karnofsky performance status (KPS) $\geq$ 70% and adequate hematologic, renal, and hepatic function. Patients who had prior chemotherapy for advanced NSCLC or who had received prior erlotinib, gefitinib, cetuximab, or trastuzumab were excluded. Patients who never smoked cigarettes were excluded.

Treatments

Patients were randomly assigned to one of the following three treatment arms (Fig 1): erlotinib 150 mg on days 1 and 2 followed by chemotherapy on day 3 (150 PRE); erlotinib 1,500 mg on days 1 and 2 followed by chemotherapy on day 3 (1,500 PRE); or chemotherapy on day 1 followed by erlotinib 1,500 mg on days 2 and 3 (1,500 POST). Chemotherapy for all patients was paclitaxel 200 mg/m^2 as a 3-hour infusion followed by carboplatin (area under the curve = 6) as a 30-minute infusion. Patients received up to six cycles of treatment. These were the same doses and schedules used in TRIBUTE.[8] After completion of six cycles of therapy, no maintenance erlotinib was administered. Antiemetics and dexamethasone premedication to prevent hypersensitivity reactions were administered according to institutional guidelines.

Toxicities and Dose Modifications

Grade 3 to 4 nonhematologic toxicities believed to be possibly related to erlotinib were managed with dose reductions to 100 mg for patients randomly assigned to 150 mg or to 1,050 mg for patients randomly assigned to 1,500 mg. Only a single erlotinib dose reduction was permitted per patient. Patients who had dose reductions did not have subsequent dose escalation. Grade 1 to 2 erlotinib-related diarrhea was managed with loperamide. Erlotinib-related rash was managed at the discretion of the investigator.

Paclitaxel and carboplatin dose reductions were allowed for febrile neutropenia or if the absolute neutrophil count was less than 500/μL for $\geq$ 5 days. All patients had an absolute neutrophil count $\geq$ 1,500/μL and a platelet count $\geq$ 100,000/μL before initiation of each cycle. Filgrastim and pegfilgrastim were not routinely administered but were allowed at the discretion of the treating physician.

Study Evaluation

Computed tomography scans of previously unirradiated, Response Evaluation Criteria in Solid Tumors–defined, measurable sites of disease were obtained at baseline and after cycles 2, 4, and 6. Before each treatment, patients underwent a medical history, physical examination, CBC, and chemistry panel.

Biostatistics

The primary end point of this study was overall response rate using Response Evaluation Criteria in Solid Tumors. Secondary end points were time to progression, survival, and clinical adverse events. A Simon two-stage design was used in which a 20% response rate was considered insufficient to

warrant further investigation and a 50% response rate was considered desirable. The type I and type II error rates were both 5%, with a power of 95%. For each arm, 14 patients were enrolled onto the first stage. If there were four responses in an arm, that arm expanded to accrue a total of 29 patients. If 10 responses were observed in a treatment arm of 29 patients, then further study of that treatment was considered to be warranted. If more than one treatment arm met the primary end point of 10 responses, then the arm with the highest overall number of responses would be chosen for further evaluation (a pick the winner approach).

Time to event analyses (survival and time to progression) were performed using Kaplan-Meier analysis. Patients who were alive at the time of analysis were censored at the date of last evaluation. Patients who began additional therapy before radiographic evidence of disease progression were censored as of the date of the new treatment. Patients who died without documented disease progression were censored at the time of the last evaluation. Log-rank testing was used to compare the overall survival and time to progression distributions for the three treatment arms.

RESULTS

Baseline Characteristics

Between November 15, 2004 and November 14, 2006, 87 patients were enrolled and randomly assigned to one of the three treatment arms (150 PRE, 1,500 PRE, or 1,500 POST). Patients were treated at Memorial Sloan-Kettering Cancer Center (New York, NY; n = 58) or the Sidney Kimmel Comprehensive Cancer Center (Baltimore, MD; n = 29). One patient randomly assigned to the 150 PRE arm did not receive treatment as a result of progression of disease. This patient was not included in the analysis. Baseline characteristics for patients by treatment arm are listed in Table 1. There were no statistically significant differences with regard to age, sex, performance status, and sites of metastases. Numerically, there were more patients with brain metastases in the 1,500 POST arm, and there were more men in the 1,500 PRE arm. Although there were equivalent numbers of patients with a KPS of 80% in each arm, there were fewer patients with a KPS of 70% in the 1,500 PRE arm.

Table 1. Baseline Patient Characteristics

Characteristic	150 PRE (n = 28)	1,500 PRE (n = 29)	1,500 POST (n = 29)
Age, years			
Median	68	62	62
Range	51-81	42-78	43-81
Sex, No. of patients			
Female	15	13	15
Male	13	16	14
KPS, No. of patients			
70%	4	1	4
80%	11	11	12
90%	13	17	13
Histology, % of patients			
Adenocarcinoma	54	62	52
Squamous	4	3	17
NSCLC*	43	35	31
Brain metastases, % of patients	17	14	31
Bone metastases, % of patients	31	41	24

Abbreviations: 150 PRE, erlotinib 150 mg on days 1 and 2 followed by chemotherapy on day 3; 1,500 PRE, erlotinib 1,500 mg on days 1 and 2 followed by chemotherapy on day 3; 1,500 POST, chemotherapy on day 1 followed by erlotinib 1,500 mg on days 2 and 3; KPS, Karnofsky performance status; NSCLC, non–small-cell lung cancer.
*Refers to NSCLC not further characterized.

Treatment

Patients received a median of four cycles of treatment. There were no differences in the number of cycles of treatment administered based on treatment arm.

Efficacy

Efficacy outcomes are listed in Table 2. The cohort of patients treated with erlotinib 1,500 mg before carboplatin and paclitaxel (1,500 PRE arm) met the prespecified end point of 10 responses. Patients treated with 1,500 PRE had the longest overall survival time, with a median survival time of 15 months. None of the differences in overall survival (Fig 2A), time to progression (Fig 2B), or response rate (Fig 3) for the three treatment arms reached statistical significance.

Toxicity

The most common toxicities are listed in Table 3. There were no statistically significant differences between treatment arms. Grade ≥ 3 rash and diarrhea were uncommon. Seven patients required dose reductions of erlotinib (two patients in the 1,500 PRE arm and five patients in the 1,500 POST arm). The reasons for erlotinib dose reduction were grade 3 diarrhea (n = 3), syncope (n = 1), grade 2 mucositis (n = 1), grade 2 hyperbilirubinemia (n = 1), and persistent grade 2 rash (n = 1). Sixteen patients had dose reductions of carboplatin, paclitaxel, or both carboplatin and paclitaxel (four patients in the 150 PRE arm, nine patients in the 1,500 PRE arm, and three patients in the 1,500 POST arm).

Molecular Characteristics

Although tissue for *EGFR* and *KRAS* mutation testing was not required for entry onto this protocol, *EGFR* mutation results were available for 11 patients, and *KRAS* mutation results were available for two patients. A single patient had an *EGFR* L858R mutation. This patient was treated with 1,500 PRE and had stable disease as best

Table 2. Response to Treatment

Response	150 PRE (n = 28)	1,500 PRE (n = 29)	1,500 POST (n = 29)
Median No. of cycles	4	4	4
No. of responders	5	10	8
Response rate, %	18	34	28
95% CI	6 to 37	18 to 54	13 to 47
Overall survival, months			
Median	10	15	10
95% CI	8 to 16	8 to NR	5 to 16
1-year survival rate, %	49	63	48
2-year survival rate, %	25	42	26
Time to progression, months			
Median	4	4	5
95% CI	3 to 5	3 to 6	3 to 8

Abbreviations: 150 PRE, erlotinib 150 mg on days 1 and 2 followed by chemotherapy on day 3; 1,500 PRE, erlotinib 1,500 mg on days 1 and 2 followed by chemotherapy on day 3; 1,500 POST, chemotherapy on day 1 followed by erlotinib 1,500 mg on days 2 and 3; NR, not reached.

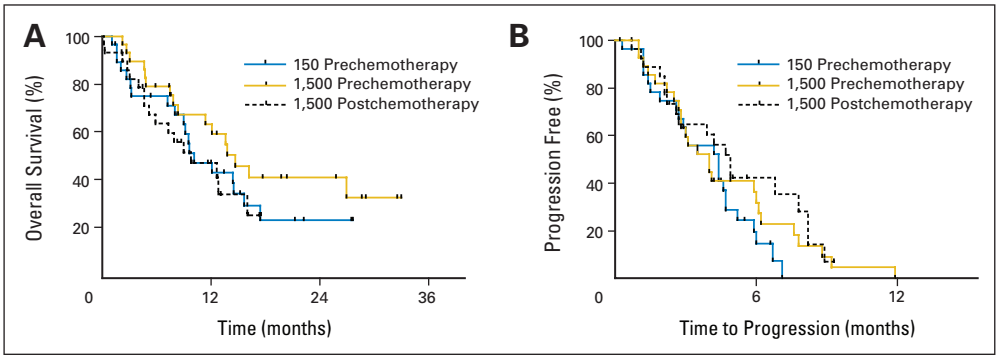

Fig 2. (A) Overall survival. (B) Time to progression. 150 PRE, erlotinib 150 mg on days 1 and 2 followed by chemotherapy on day 3; 1,500 PRE, erlotinib 1,500 mg on days 1 and 2 followed by chemotherapy on day 3; 1,500 POST, chemotherapy on day 1 followed by erlotinib 1,500 mg on days 2 and 3.

response. One patient treated with 150 PRE had a *KRAS* G12V mutation. This patient had stable disease as best response.

Second-Line Therapy

Although data were not routinely collected for additional lines of therapy, we obtained information about therapy after progression of disease for 48 patients. Similar rates of second-line chemotherapy administration were noted for all treatment arms, with 67% of patients (14 of 21 patients) in 150 PRE arm, 71% of patients (10 of 14 patients) in 1,500 PRE arm, and 69% of patients (nine of 13 patients) in 1,500 POST arm receiving second-line therapy.

DISCUSSION

This randomized phase II study assessed the efficacy and toxicity of three schedules combining erlotinib with carboplatin and paclitaxel. In these former or current smokers, who were selected to enrich the

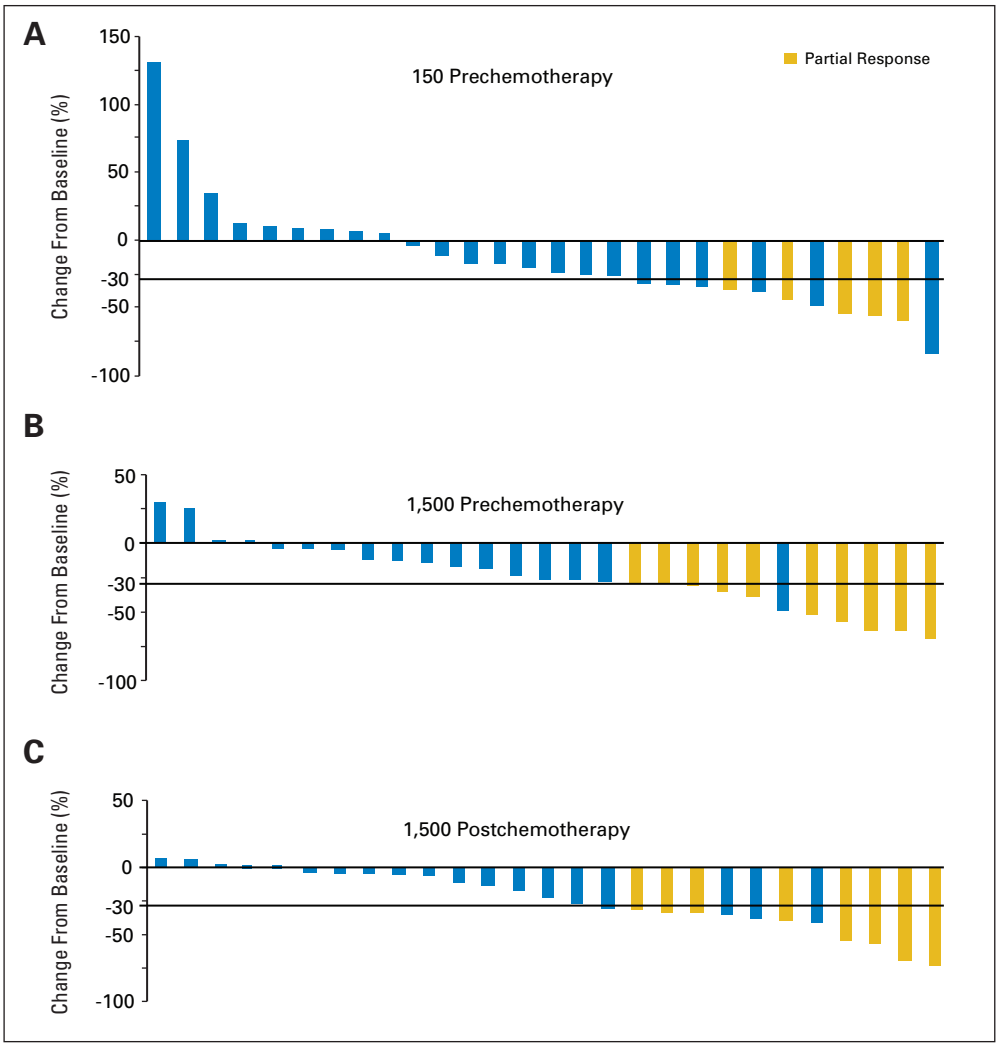

Fig 3. Maximal reduction for indicator lesions (Response Evaluation Criteria in Solid Tumors) for patients treated with (A) erlotinib 150 mg before chemotherapy (150 PRE), (B) erlotinib 1,500 mg before chemotherapy (1,500 PRE), and (C) erlotinib 1,500 mg after chemotherapy (1,500 POST).

Table 3. Treatment-Related Toxicities

Toxicity	No. of Patients					
	150 PRE		1,500 PRE		1,500 POST	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	4	5	6	9	3	8
Anemia	2	0	0	0	2	0
Thrombocytopenia	0	2	1	1	0	0
Neuropathy	1	0	3	0	1	0
Thrombosis	2	1	2	0	2	0
Fatigue	2	1	3	0	4	0
Dyspnea	2	1	2	0	2	0

Abbreviations: 150 PRE, erlotinib 150 mg on days 1 and 2 followed by chemotherapy on day 3; 1,500 PRE, erlotinib 1,500 mg on days 1 and 2 followed by chemotherapy on day 3; 1,500 POST, chemotherapy on day 1 followed by erlotinib 1,500 mg on days 2 and 3.

study population of individuals less likely to have tumors harboring *EGFR* sensitivity mutations, we showed that treatment with erlotinib 1,500 mg for 2 days before the administration of carboplatin and paclitaxel had a numerically superior response rate, median overall survival time, and 1-year survival rate.

By administering erlotinib intermittently, we demonstrated that high-dose erlotinib (1,500 mg/d) could be administered safely in combination with carboplatin and paclitaxel, with toxicities similar to those observed previously with combinations of erlotinib and carboplatin and paclitaxel.[8] Among the treatment arms, there were no statistically significant differences in a variety of toxicities. However, the numerically more frequent grade 3 and 4 neutropenia in the 1,500 PRE arm led to more chemotherapy dose reductions in this treatment arm (nine dose reductions in the 1,500 PRE arm *v* four for the 150 PRE arm and three in the 1,500 POST arm). Despite the dose reductions in chemotherapy, this arm had the highest response rate and longest overall survival.

To improve on standard chemotherapy doublets used to treat advanced NSCLC, investigators have empirically combined targeted therapies with conventional regimens, most commonly carboplatin and paclitaxel. The single successful example of this strategy is the improvement in response and survival associated with the addition of bevacizumab to carboplatin and paclitaxel.[21] A key factor in this success was the solid statistical design of the Eastern Cooperative Oncology Group 4599 trial based on data obtained from a randomized phase II trial conducted to choose regimens for the definitive test in phase III.[22] In sharp contrast, the statistical designs for the failed phase III studies combining EGFR inhibitors with chemotherapy were not based on a well-conducted phase II study. As an example, the phase II outcomes seen with the combination of continuous daily gefitinib with carboplatin and paclitaxel were not used to design the Iressa NSCLC Trial Assessing Combination Treatment study. The observed benefits were insufficient to justify further study in phase III[23] and ultimately predicted the results seen with this regimen in the failed phase III trial.[7] The preclinical underpinnings for this trial were also inadequate. Although the trial tested continuous daily gefitinib administered with chemotherapy, the preclinical experiments used in part to justify the study administered gefitinib to mice on Monday through Friday, with the chemotherapy administered only on Monday.[6] With the more rapid elimination of gefitinib seen in mice compared with humans, effectively, there was no gefitinib present when the chemotherapy was administered. Moving forward, the experience combining targeted agents with standard chemotherapy in NSCLC provides powerful lessons to guide the development of an increasing number of targeted agents now available for testing.

This trial was conceived to serve as a basis to decide how this concept and a specific regimen should be advanced to a phase III study. We had strong preclinical data to support the hypothesis.[16] We also attempted to accurately replicate the conditions of the preclinical experiment in patients with close attention to issues of erlotinib schedule and dose. The availability of the TRIBUTE database and our adherence to the protocol specifications of TRIBUTE in patient selection and treatment gave us confidence that we could reliably use the available data from the carboplatin plus paclitaxel alone arm as a benchmark. We also used this opportunity to test the clinical utility of erlotinib treatment after chemotherapy, a concept being developed by us in tandem with other research teams.[17,18,24]

Patients receiving erlotinib 1,500 mg daily for 2 days before chemotherapy (1,500 PRE) had a response rate of 34%, a median survival time of 15 months, and a 1-year survival rate of 62%. It was the only arm to meet the prespecified statistical end point of 10 responses. We recommend that this regimen (using the same dose and schedule of erlotinib followed by carboplatin and paclitaxel) be compared with carboplatin and paclitaxel in a randomized phase III trial among former or current smokers. In the TRIBUTE trial, 495 former or current smokers receiving carboplatin and paclitaxel alone had a response rate of 20%, a median overall survival time of 11 months, and a 1-year survival rate of 41% (data on file, Genentech, South San Francisco, CA).

We would propose a phase III study to document a 4-month improvement in median overall survival time, from 11 to 15 months. Complicating our design calculations is the demonstration that bevacizumab can improve the median overall survival of eligible patients with nonsquamous lung cancer by 2 months.[21] Therefore, we would propose to add bevacizumab as appropriate to both arms of the proposed phase III study. We estimate that 50% of participants would be candidates for bevacizumab and, furthermore, that the addition of bevacizumab to treatment for half of the patients on both study arms would increase the median overall survival time by 1 month in each arm. Thus, we estimate a median overall survival time of 12 months in the control arm and 16 months in the intervention arm. To demonstrate this improvement in median overall survival, 492 events would be needed. We would stratify participants based on sex, performance status, and bevacizumab administration. Although there is substantial evidence that bevacizumab can be safely combined with erlotinib and clinical experience with all four agents administered together, we plan an early look to assess for additional or unexpected toxicities with the addition of bevacizumab in these patients.

Attempting to replicate laboratory experiments in the clinic, this trial explored the consequences of altering the dose and schedule of erlotinib in combination with cytotoxic chemotherapy in persons with NSCLC. In this randomized phase II trial, the highest response rate was seen in patients treated with high-dose erlotinib daily for 2 days before carboplatin and paclitaxel. The mechanism behind the enhanced effectiveness of the combination by alteration of the schedule is not clear. By using intermittent dosing, this schedule allowed the administration of erlotinib at higher doses, which may have increased inhibition of wild-type EGFR, leading to greater antitumor effect. It is

also possible that administration of higher doses of erlotinib leads to inhibition of off-target kinases.[25,26] Inhibition of these targets, in combination with chemotherapy, may lead to added benefit. Another possibility is that administration of anti-EGFR treatment in combination with chemotherapy leads to inhibition of angiogenesis, as has been seen in some models with gefitinib.[27]

This study was designed to provide the framework for further investigation of intermittent erlotinib in combination with chemotherapy and was not a definitive evaluation of this treatment. The sample size enrolled onto each arm leads to overlap in the CIs for all efficacy end points (response rate, time to progression, and overall survival). We did not enroll a separate control arm but, instead, compared our results with the hundreds of former or current smokers treated with carboplatin and paclitaxel as part of TRIBUTE. Although we used the same entry criteria and treatment as we did in TRIBUTE, our study was conducted 3 years later at two institutions, raising the possibility of small differences in the patient population treated. As with many small randomized trials, there were numerical imbalances in the baseline characteristics of patients in treatment arms. The differences in these characteristics were often counterbalanced. For example, although the 1,500 PRE arm had more patients with a KPS of 90%, it also had the largest proportion of men and individuals with bone metastases. Although the results of this randomized phase II trial are, by themselves, insufficient to recommend adoption of pulsed erlotinib as a standard treatment, they do provide sufficient preliminary data to justify and design a rigorous phase III test of the 1,500 PRE regimen.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Gregory J. Riely, Genentech (C), Hoffman-La Roche Inc (C); Mark G. Kris, Genentech (C); Julie R. Brahmer, Genentech (C); Vincent A. Miller, Genentech (C), OSI Pharmaceuticals (C); Charles M. Rudin, Genentech (C) **Stock Ownership:** None **Honoraria:** Daniel T. Milton, Genentech **Research Funding:** Gregory J. Riely, Genentech; Naiyer A. Rizvi, Genentech; Christopher G. Azzoli, Genentech **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: Naiyer A. Rizvi, Mark G. Kris, Daniel T. Milton, David B. Solit, Neal Rosen, Francis M. Sirotnak, Venkatraman E. Seshan, Vincent A. Miller, Charles M. Rudin
Financial support: Mark G. Kris, Charles M. Rudin
Administrative support: Naiyer A. Rizvi, Mark G. Kris, Charles M. Rudin
Provision of study materials or patients: Naiyer A. Rizvi, Mark G. Kris, Christopher G. Azzoli, Julie R. Brahmer, Vincent A. Miller, Charles M. Rudin
Collection and assembly of data: Gregory J. Riely, Naiyer A. Rizvi, Mark G. Kris, Daniel T. Milton, Emir Senturk, Julie R. Brahmer, Venkatraman E. Seshan, Margaret Fogle, Michelle Ginsberg, Vincent A. Miller, Charles M. Rudin
Data analysis and interpretation: Gregory J. Riely, Naiyer A. Rizvi, Mark G. Kris, Venkatraman E. Seshan, Charles M. Rudin
Manuscript writing: Gregory J. Riely, Naiyer A. Rizvi, Mark G. Kris, Vincent A. Miller, Charles M. Rudin
Final approval of manuscript: Gregory J. Riely, Naiyer A. Rizvi, Mark G. Kris, Daniel T. Milton, David B. Solit, Neal Rosen, Emir Senturk, Julie R. Brahmer, Margaret Fogle, Michelle Ginsberg, Vincent A. Miller, Charles M. Rudin

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